Transient Hematuria in an Adolescent Male Treated with Increased Doses of Methylphenidate

Artan Dozda Metilfenidat ile Tedavi Edilen Bir Erkek Ergende Oluşan Geçici Hematüri

Abstract

In this report we presented the case of an adolescent male who noticed bloody spots on his underwear after the dose increase during his osmotic-controlled release oral delivery system-methylphenidate (MPH) treatment. This symptom disappeared when the MPH treatment was discontinued, was not reported with atomoxetine monotherapy, but reoccurred with combination treatment using atomoxetine and increased doses of immediate-release MPH. We discussed the clinical picture and the possible pathophysiological mechanisms for this adverse effect.

Keywords: hematuria; methylphenidate; adverse effect

Öz

Bu yazıda, ozmotik kontrollü salınım oral uygulama sistemi-metilfenidat (MF) tedavisindeki doz artırımının ardından iç çamaşırında kanlı lekeler fark eden bir erkek ergen sunulmuştur. Bu belirti, MF tedavisinin kesilmesiyle kaybolmuş, atomoksetin monoterapisi ile ortaya çıkmamış, ancak atomoksetin ve artırılmış dozdaki hızlı salınımlı MF kombinasyonuyla yeniden ortaya çıkmıştır. Bu klinik tablo ve olumsuz etkinin olası patofizyolojik mekanizmaları tartışılmıştır.

Anahtar Sözcükler: hematüri; metilfenidat; yan etki

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INTRODUCTION

Methylphenidate has been the first line psychopharmacological treatment in children as well as in adolescents with ADHD, and results in significant improvement in 70 to 80% of the affected children. Nausea, decreased appetite, weight loss, and sleep disturbances are among the most frequently reported adverse effects during treatment with MPH (1). Besides these common adverse effects, MPH has also been reported to cause some unusual adverse effects, such as hallucinations, hypersexuality and inappropriate sexual behaviors, priapism, skin eruptions, excessive menstrual bleeding, obsessive–compulsive symptoms, gynecomastia, hyperhidrosis, painful muscle cramps, and cholelithiasis (2–8). However, as far as we know there is no reported case of hematuria associated with MPH in children and adolescents with ADHD. Therefore, our case seems to be a first case in the literature on MPH treatment-related hematuria.

CASE

An 18-year-old male had been diagnosed with attention deficit hyperactivity disorder (ADHD) inattentive presentation and special learning disorder and followed up since the age of eight. He had been under osmotic-controlled release oral delivery system (OROS) MPH (18–54 mg/day) treatment for almost 10 years, with considerable improvement in his ADHD symptoms. Although he generally tolerated OROS-MPH well, he reported some level of decreased appetite and emotionality. He had been taking OROS-MPH (54 mg/day) for the last two years, although he did not receive medication during summer holidays. His weight and height were 58 kg and 171 cm when his OROS-MPH treatment was initiated. He started to report occasional bloody spots (approximately 4x4 cm in size) on the front side of his underwear after the OROS-MPH dose was increased to 54 mg/day. He reported no blood while or just after urinating, but seeing bloody spots the next time he went to the toilet. He also reported occasional difficulty and burning sensation during urination in the first month of the OROS-MPH treatment. However, while the burning sensation and difficulty disappeared in time, he continued to report bloody spots. During ten months of OROS-MPH (54 mg/day) treatment, he reported bloody spots almost 20 times. At two different times he underwent detailed medical examinations, including urinary system ultrasonography, X-rays, complete urine and blood analyses, and bleeding tests, which revealed no clear reason for the spots. The symptoms of difficulty and burning sensation during urination were absent at the time of the first medical evaluation, during which no significant problem was recorded, and depending on his medical history it was thought that the patient might have developed urinary tract infection. Despite the lack of clinical or laboratory evidence, antibiotic treatment was recommended, but the patient's parents did not comply after consulting another doctor. The parents confirmed the bloody spots on the patient's underwear and several photos of them seen by clinicians. Interestingly, the patient did not report any spot during the two-month medication-free period in his summer holiday. During the school term he received OROS-MPH treatment (27 mg/day) again. He did not report any bloody spot during the two months when he took OROS-MPH at 27 mg/day. However, he restarted to report bloody spots when the dose was increased to 54 mg/day. He continued to be treated with OROS-MPH (54 mg/day) for 6 months, with bloody spots appearing once or twice a month. He was then referred to another urologist, who could reveal no significant underlying pathology. Despite the fact that his ADHD symptoms showed substantial improvement with MPH, the patient was recommended to switch to atomoxetine. His treatment with atomoxetine was initiated at a dose of 25 mg/day, which was titrated up to 80 mg/day five months later. He was advised to continue his medication during the summer holiday as well. He generally tolerated atomoxetine well, with no report of bloody spots during eight months of treatment with atomoxetine (25–80 mg/day). However, he reported some attention problems during schooltime, particularly during the exams. He was then advised to take immediate-release (IR) MPH (10 mg) once or twice a day in combination with atomoxetine (80 mg/day). He reported no bloody spots during the one month when he was on atomoxetine (80 mg) and IR MPH (20 mg) combination treatment. However, he reported, three times in ten days, bloody spots on his underwear when he took IR MPH at 40 mg/day during his exam period.

He was advised to decrease the dose to a maximum of 20 mg/day. During the three-month follow-up period he reported no spot with atomoxetine (80 mg) and IR MPH (10–20 mg) combination treatment. Previously he did not have any significant medical problem and did not use any drug or herbal medicine. His blood pressure and pulse were within normal limits in different measurements performed while he was on and off medication. There was no history of genital trauma that might cause such symptoms. The patient and his parents gave verbal assent and consent for the publication of this paper.

DISCUSSION

MPH is generally well tolerated with several frequent side effects that are generally transient and do not require discontinuation of the treatment (1). However, as mentioned previously, a number of adverse effects have also been reported with MPH in children and adolescents with ADHD. As far as we know, there is no report of MPH-related hematuria in the literature. In this report we presented the case of an adolescent male who developed hematuria while under treatment with MPH. It is important to note that hematuria in this case occurred after the MPH dose was increased to 54 mg/day and that the symptoms improved during the medication-free periods. Given the fact that hematuria reoccurred after the dose was re-increased to 54 mg/day and did not occur during eight months of ATX monotherapy and then reoccurred with ATX and MPH combination treatment, we can suggest that the hematuria in this case was linked with the MPH treatment as the medical investigations could not reveal another reason. Causality assessment using the Naranjo Adverse Drug Reaction Scale revealed a score of 7, showing probable causality (9).

Bleeding problems have been reported as a common cause of macroscopic hematuria (10). MPH has been reported as a possible cause of thrombocytopenia that may cause any type of bleeding (11). One possible mechanism is that OROS-MPH might have caused or triggered hematuria in this case by causing a kind of bleeding diathesis such as thrombocytopenia (11). However, the patient had no history of abnormal bleeding and his hemogram and bleeding tests during the OROS-MPH treatment were normal. For this reason, we believe that the hematuria in our case was not related to a bleeding abnormality. Another possible reason is hypertension as OROS-MPH has been associated with increased blood pressure through central dopaminergic and peripheral noradrenergic actions (12,13). However, the patient's blood pressure was seen to be within normal limits in different measurements performed while he was on or off medication, which indicates that this is not the mechanism of the MPH-related hematuria developed in this case. Penile trauma is another possibility in such cases, but we excluded this cause as there was no history of genital trauma (10). A review of the literature on drug-induced hematuria showed that macroscopic hematuria might be the result of dryness in or injury to the urinary tract mucosa (14,15). There are several case reports of hematuria following isotretinoin and carboplatin use, possibly due to such dryness or injury, respectively. Hematuria in these cases was considered to be drug-related as other possible causes were excluded in the light of detailed medical history and laboratory workup (14,15). It is possible that MPH caused hematuria in our case via these mechanisms as various possible factors and causes were investigated and excluded at several different occasions. However, despite the strong causal link between OROS-MPH and hematuria in our case, it is unclear through which pathophysiological mechanisms OROS-MPH might have caused this adverse effect. Whatever the underlying pathophysiological mechanism, such unusual adverse effects can pose significant distress to the patients and their parents, complicating treatment compliance. Clinicians treating children with ADHD should be familiar with rare MPH treatment-related side effects.

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